UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/375,609	08/17/1999	LAWRENCE A. RHEINS	DERM1100-1	5338

7590 12/12/2002

LISA A. HAILE
GRAY CARY WARE & FRIEDENRICH
4365 EXECUTIVE DRIVE SUITE 1600
SAN DIEGO, CA 92121

EXAMINER
SPECTOR, LORRAINE

ART UNIT	PAPER NUMBER
1647	25

DATE MAILED: 12/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.

EXAMINER

ART UNIT	PAPER NUMBER
	25

DATE MAILED:

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 8/29/02 & 10/1/02

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 11-65, 70-95, 97-106, 111-149 is/are pending in the application.
Of the above, claim(s) 11-63 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 64, 65, 70-95, 97-106, 111-149 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☒ Claim(s) 11-65, 70-95, 97-106, 111-149 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

Part III: Detailed Office Action

Notice: Effective June 18, 2000, the Examiner examining and Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner Lorraine Spector, in Group Art Unit **1647**.

The request filed on 5/13/02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/375609 is acceptable and a CPA has been established. An action on the CPA follows.

Newly introduced claim 156 has been renumbered as 149. See 37 C.F.R. § 1.126.

Claims 11-65, 70-95, 97-106 and 111-149 are pending. Claims 11-63 remain withdrawn from prosecution as being drawn to a non-elected invention, election having been made without traverse in paper number 6, filed 11/17/00.

Formal Matters:

Claims 65 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 65 fails to further limit claim 64, as any sample of skin would necessarily comprise one or more of the recited cell types.

Claim 115 fails to further claim 104, from which it depends because claim 104 states that the skin sample is obtained using an adhesive, and does not encompass scraping.

The use of the trademark "Scotch™ tape" has been noted in this application and in the

claims. It should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. In this case, as no particular type of Scotch™ tape is envisioned or disclosed, the Examiner objects to the use of the trademarked term, as it is not being used to indicate any single particular product, e.g. in this case, relevant to the claimed invention, any single type or class of adhesive tape. There are innumerable tapes sold under the brand name Scotch™ tape, including rubber electrical, corrosion protection, insulating and sealing, splicing, lint-removing, masking, film, etc. (source, www.3M.com). Accordingly, the mere use of the term Scotch™ tape does not denote any particular product or property.

The specification provides no information that would breathe life and meaning into the term "non-invasive." Accordingly, the Examiner has turned to an online dictionary to determine the common meaning of the term. The Merriam-Webster website (http://m-w.com/) provides the definition of noninvasive as meaning "not involving penetration (as by surgery or hypodermic needle) of the skin of the intact organism". Stedman's Medical Dictionary (27th ed.) defines noninvasive as "Denoting a procedure that does not require insertion of an instrument or device through the skin or a body orifice for diagnosis or treatment. " Therefore, the claims have been interpreted to indicate that the skin may be scraped or removed via adhesive, but may not be fully breached, e.g. that at least some portion of the basal stratum remains intact.

Double Patenting:

It is noted that this application has many divisional applications from which priority is claimed. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is reminded to either cancel the conflicting claims from all but one application

or maintain a clear line of demarcation between the applications. See MPEP § 822.

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 73, 74, 76-83, 89-91, 94, 98-100, 102, 104-106 and 111-135, 137-149 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims such as claim 64, 104 and 135 that state that adhesive is applied "in a manner such that the skin nucleic acid profile after application is not affected for up to two hours" are indefinite, as it is not clear what method steps are implied by that limitation, e.g. what the envisioned "manner" is. The specification fails to provide information to breathe life and meaning into such, as there is no discussion as to *how* the adhesive is to be applied.

All claims that refer to tape are indefinite, as it is not clear what limitation is intended. There are innumerable tapes sold under the brand name Scotch™ tape, including rubber electrical, corrosion protection, insulating and sealing, splicing, lint-removing, masking, film, etc. (source, www.3M.com). It is not clear what feature is intended by the recitation of the term

Claims 74 and 114 contain the trademark/trade name Scotch™ . Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe "Scotch™ tape". Various Scotch™ brand tapes have various different properties, and many have functional equivalents, as evidenced by the tables of equivalents available at the 3M website. Accordingly, the

identification/description is indefinite.

There is no antecedent basis for "the adhesive surface" of claim 64, as recited in claim 73.

Claims 76-84, 89-91, 98-100, 116-127, 135 and 137-148 are indefinite because each of the claims recites a property of the nucleic acid, or in the case of claim 89 the claim recites a desired result, however such are not method steps. It is not clear how the claimed methods themselves are further limited by the recitation of properties of the nucleic acids or result.

Claim 94 is indefinite as there is no antecedent basis in claim 64 for "the cellular material sample".

Claim 102 is indefinite for omitting essential steps. There is no step claim 95 that would generate a "complementary equivalent" to the isolated nucleic acid.

Claim 104 is further indefinite as the preamble specifically states that the method if for "use in isolating or detecting nucleic acid *encoding a cytokine*", however there are no method steps nor reference in the claim to a nucleic acid encoding a cytokine; the claim fails to achieve the goal set forth in the preamble.

Claim 135 is indefinite for reciting "after application" in line 5, as it is not clear what has been applied, or when.

Claim 149 is indefinite for being self-referential. The claim as submitted was numbered as 156, and has been renumbered under Rule 126 as claim 149. However, as submitted, the claim depends from claim 149. There having been no previously pending claim 149, the dependency of the claim cannot be changed under Rule 126. As the metes and bounds of the claim cannot be determined, it will not be considered further under 35 U.S.C. § 112, first paragraph or in the consideration of the prior art.

The remaining claims are rejected for depending from an indefinite claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 64, 65, 70-84, 104-135 and 137-148 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 64, 104 and 135 state "in a manner such that the skin nucleic acid profile after application is not affected for up to about two hours". There is no basis for this limitation in the specification as originally filed. The only relevant disclosure appears at page 8 line 7 and again at page 18, lines 8, and states "The process of tape stripping itself has been shown not to affect the skin cytokine profile during the first few hours after the procedure is done." Such does not provide basis for the current limitations as drawn to tape stripping, and there is no basis in the specification as originally filed for a method of scraping the skin in which the cytokine profile remains unaffected, as claimed in claim 135.

With further respect to claims 71, 72, 106 and 112, there is no basis in the specification for stripping the skin only a single time, or 1-2 times. The specification discloses only "The skin is stripped up to a maximum of 25 times", as found at page 18, line 4, and there is no evidence of conception of criticality of stripping the skin only one or two times. It is noted that claim 70 does not introduce new matter, as the recitation of "between one and twenty-five times" is consistent with the disclosure in the specification of "The skin is stripped up to a maximum of 25 times", as found at page 18, line 4.

Claims 64, 65, 70-84, 104-135 and 137-148 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is on the basis that the

specification as originally filed does not adequately describe the claimed invention.

As stated above, claims 64, 104 and 135 state "in a manner such that the skin nucleic acid profile after application is not affected for up to about two hours". There is no basis for this limitation in the specification as originally filed. The only relevant disclosure appears at page 8 line 7 and again at page 18, lines 8, and states "The process of tape stripping itself has been shown not to affect the skin cytokine profile during the first few hours after the procedure is done."

There is no written description of which 'process of tape stripping' does not affect the skin cytokine profile- it is noted that some of the claims are limited to 1-2 repetitions, whereas others include up to 25. Also, tapes with various adhesive strengths are encompassed, from the most gentle to the most 'sticky', such as duct tape; there is no description of what type of tape does not affect the skin cytokine profile. There is no description of the 'manner' in which the tape may be used without affecting the skin cytokine profile. Finally, there is absolutely no written description in the specification as filed of any 'manner' in which the skin may be scraped to obtain a sample without affecting the skin cytokine profile; see claim 135.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 64-65, 70-72, 76-95, 98-106, 111-114, 116-148 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for (a) isolating stratum lucidum, stratum granulosum, stratum spinosum or stratum basale cells using adhesive tape

(claim 104), including a single application of such (claim 106) (b) isolating cells "in a manner such that the skin nucleic acid profile after application is not affected for up to about two hours", either with adhesive tape or by scraping (claim 135),(c) non-tape adhesives(d) detection of DNA or (e) detection of IL-2, IL-5 or IL-13, leukotriene or prostaglandin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Each of the above grounds will be addressed in turn:

(a) Enablement is not commensurate in scope with claims to isolating stratum lucidum, stratum granulosum, stratum spinosum or stratum basale cells using adhesive tape (claim 104), including a single application of such (claim 106).

It is credible that one could obtain stratum corneum cells using a single application of adhesive tape. However, the four innermost layers of skin, the stratum lucidum, stratum granulosum, stratum spinosum and stratum basale lay under the stratum lucidum, and would seem not to be sufficiently accessible to the adhesive tape to be removed with a limited number of applications. The nature of the invention is the use of tape to remove cells for the purpose of assaying nucleic acids in those cells. The prior art of record (van der Molen, Arch. Dermatol. Res. 289:514-518 and Nickoloff et al., Clin. Immunol. and Immunopath 73:63-68), indicates that one would expect to obtain only stratum corneum cells with up to 25 tape strippings, and does not provide guidance as to how to obtain the inner four cell layers using tape. There is no guidance in the specification as to which cell types are obtained with what types of tape application (type of tape, repetition, etc.) nor is there a single working example in which the cell types obtained were

examined. Given the lack of recognition in the art and the absence of guidance or working examples, it would require undue experimentation to determine under what conditions the various cell types could be obtained using adhesive tape stripping, and it is not predictable that such could be obtained under *any* condition using only a very limited number of strippings. Accordingly, enablement is not commensurate in scope with claims to isolating stratum lucidum, stratum granulosum, stratum spinosum or stratum basale cells using adhesive tape (claim 104), including a single application of such (claim 106).

(b) Enablement is not commensurate in scope with claims to isolating cells from the skin "in a manner such that the skin nucleic acid profile after application is not affected for up to about two hours", either with adhesive tape or by scraping.

The nature of the invention is the removal of cells for the purpose of assaying nucleic acids in those cells, without affecting the cytokine profile of the skin that provides said cells. The prior art of record (Nickoloff et al., Clin. Immunol. and Immunopath 73:63-68) indicates that one would expect the cytokine profile of the skin to be altered by tape application. This would lead the person of ordinary skill in the art to expect the same of scraping, which is mechanically more destructive than taping. The specification asserts that "The process of tape stripping itself has been shown not to affect the skin cytokine profile during the first few hours after the procedure is done", but provides no data in support of such, no working examples, and no guidance as to under what conditions such a result may be obtained. It is noted, however, that it would seem logical that a single application of tape or scraping to remove a shallow layer of stratum corneum would probably achieve that effect, as the stratum corneum is not a 'living' layer of tissue, but is made up, especially in the outermost layers, of flattened remnants of cells completely filled with keratin. However, the remaining layers of skin are living, and it would not be predictable that they could be perturbed without obtaining a cytokine response; in fact, the prior art teaches the opposite. Accordingly, given the contrary expectations in the prior art and the lack of guidance or working examples, the specification enabling only for the removal of stratum corneum without affecting the cytokine profile of the skin, and is not

enabling of the full scope of removal of cells without affecting the cytokine profile of the skin.

(c) Enablement is not commensurate in scope with claims to the use of adhesives that are in a form other than tape.

The claims encompass non-tape adhesives. For example, claim 64 merely states "an adhesive", and is further limited by claim 73, which states that the adhesive is an adhesive tape. The state of the art is that it is known to use adhesive tapes to obtain skin samples, however no other form of adhesive could be found by the Examiner to be used thusly. The specification provides no guidance nor working examples of a non-tape adhesive. The use of a non-tape adhesive would be complicated, as it is not clear how the adhesive would be applied to the skin, how it would be removed, and how the skin cells/nucleic acids would be extracted from it. Accordingly, it would require undue experimentation to determine how to use the claimed invention in its full scope.

(d) Detection of DNA: While the prior art appreciates the detection of RNA, specifically mRNA as an indicator of expression of cytokines (or other proteins), the DNA that is transcribed to make the mRNA would not be expected to be present in any different quantity when the gene is expressed, as opposed to when it is not. It is not accepted in the art that cytokine expression happens via DNA amplification, rather the DNA is transcribed to make mRNA, which is translated to make protein. Amplification (the production of protein in an amount disproportionate to the amount of DNA present) can happen either at the transcription or translation step, and often at both. Accordingly, since the person of ordinary skill in the art would not accept that DNA levels would be indicative of cytokine expression, and as the specification provides no guidance nor working examples of such, the specification is not enabling of detection of DNA for diagnosis or distinguishment of inflammatory reactions or any other disorder not directly associated with a change in the DNA itself. Further, as keratinocytes are enucleated cells, and as it is not clear that removal of any cell type in addition to keratinocytes would meet the limitation of being "in a manner" that would not affect cytokine production, it is not predictable that one could detect DNA in a sample meeting the

limitations of claim 76.

(e) Detection of IL-2, IL-5 or IL-13, leukotriene or prostaglandin: By applicants admission in the specification at page 1, it was known in the prior art at the time the invention was made that keratinocytes express IL-1, -3, -4, -6, -7, -8, -10, -12, and GM-CSF. However, it is not known that skin specifically expresses IL-2, IL-5 or IL-13. Thus, it is not predictable that expression of such can be detected, as claimed in claims 138, 141 and 146. With respect to leukotriene or prostaglandin, such are not encoded by nucleic acids, and therefore no nucleic acid encoding such can be detected. Accordingly, enablement is not commensurate in scope with those claims.

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 64, 65, 75, 77-81, 83, 85, 86, 89-91, 93, 95, 99-101, 103, 136 and 143, are rejected under 35 U.S.C. 102(b) as being anticipated by Paludan et al., J. Invest. Derm. 99:830-835, 1992.

Paludan et al. disclose obtaining skin samples by gentle scraping of the epidermis with a scalpel, via which they obtained sufficient sample to perform PCR expression analysis. See page 831, 2nd col., under "Skin Samples". They assayed for IL-8 mRNA levels, using GAPDH mRNA as an internal control. At page 834, second column, they state: "Our technique has proved useful for discriminating between epidermal IL-8 mRNA levels in a variety of inflammatory skin diseases and reactions (Fig 5, Table II) and should be applicable to analysis of other cytokine mRNAs and other skin compartments." The "variety of inflammatory skin diseases" encompassed both local and systemic reactions. Paludan specifically states that "the scraping can be done without local

anesthesia and removes most of the epidermis" (page 830). At page 834, Paludan et al. further teach that due to the small sample size needed, "Several compartments of the skin can be studied separately, such as the upper epidermis...". At the same page, they teach that "The sampling techniques also have the advantage of being rapid, and cytokine mRNAs in such samples probably reflect inherent contents and not transcriptional activation by manipulation of the tissue."They further specifically suggest detection of IFNγ mRNA (same page), and suggest the broader applicability to the study of expression of other cytokines. Accordingly, the claims are anticipated by Paludan et al.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 136 is rejected under 35 U.S.C. 102(b) as being anticipated by, or in the alternative under 35 U.S.C. 103(a) as being unpatentable over Paludan et al., J. Invest. Derm. 99:830-835, 1992.

The teachings of Paludan et al. are discussed above. Paludan did not monitor the cytokine expression patterns of the skin after scraping.

The examiner is unable to determine whether the prior art disclosures actually possesses the characteristic of not affecting the nucleic acid profile of the skin for up to two hours after scraping.

Under such circumstances, where the product seems to be identical, then the burden shifts to applicant to provide evidence that the prior art would neither anticipate nor render obvious the claimed invention. Note the case law of *In re Best* 195 USPQ 430, 433 (CCPA 1977).

Claims 137, 139-140, 142, 144, 145 and 147 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paludan et al., J. Invest. Derm. 99:830-835, 1992, in view of applicants admissions of the prior art.

The teachings of Paludan et al. are discussed above. Paludan did not specifically teach detection of nucleic acids that encode IL-1, -3, -4, -6, -7, -8, -10, -12, or GM-CSF. However, Paludan specifically suggested the broader applicability of the method to other cytokines expressed in the skin.

By applicants admission in the specification at page 1, it was known in the prior art at the time the invention was made that keratinocytes express IL-1, -3, -4, -6, -7, -8, -10, -12, and GM-CSF. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of Paludan et al. to detect other skin-expressed cytokines such as IL-1, -3, -4, -6, -7, -8, -10, -12, and GM-CSF that were well known in the art as evidenced by applicants admission of the prior art to be skin-expressed. One of ordinary skill in the art would have been motivated to do so by Paludan's suggestion of the broad applicability of the method, and would have expected success in view of Paludan's successful detection of IL-8 mRNA, which was specifically upregulated, and GAPDH mRNA, which was not. Accordingly, the invention, taken as a whole, is *prima facie* obvious over the prior art.

Claims 70-74, 97, 104-114 and 129-131 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paludan et al., J. Invest. Derm. 99:830-835, 1992 in view of van der Molen et al., Arch. Dermatol. Res. 289:514-518, previously of record.

The teachings of Paludan et al. are discussed above. Paludan does not teach or suggest taping to obtain the skin sample. However, ven der Molen et al. teach that "skin surface tape stripping with adhesive tape is a widely accepted and used method" for examining the localization and distribution of substances within the stratum corneum; see page 514, second column. They also teach that not only stratum corneum cells are so obtained, but rather cells from other layers are also obtained.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of Paludan et al. to use tape stripping instead of scraping, in view of van der Molen's disclosure that cells from multiple layers may be so obtained. The person of ordinary skill in the art would have been motivated to make the modification in view of the desirability of tape stripping as opposed to scraping, the former being less invasive and less stressful to the patient. The person of ordinary skill in the art would have expected success at making the substitution because of the teachings of Paludan et al. that only very small samples are required. With respect to claims which require a specific number of tapings, it would have been obvious and routine to determine the minimum number of strippings necessary to obtain a sufficient sample. Accordingly, the invention, taken as a whole, is *prima facie* obvious over the prior art.

Claims 87, 88 and 98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paludan et al., J. Invest. Derm. 99:830-835, 1992, in view of Frayne, U.S. Patent Number 5,811,239, and claims 116, 119, 132, and 133, are rejected under 35 U.S.C. 103(a) as being unpatentable over Paludan et al., J. Invest. Derm. 99:830-835, 1992, in view of van der Molen and further in view of Frayne, U.S. Patent Number 5,811,239.

The teachings of Paludan et al. and van der Molen are discussed above. Paludan (or Paludan in view of van der Molen) did not specifically teach detection of DNA, the use of hybridization, or RNase protection assays.

Frayne teaches that it was well known in the art to detect DNA sequence variation for the

purpose of identifying genetic disease, genetic linkage studies, identity determination, etc. She further teaches that PCT, hybridization and RNase protection are well known techniques for doing so (see paragraph bridging columns 1-2).

The person of ordinary skill in the art would immediately grasp that isolation of skin cells from layers below the stratum corneum, as suggested by Paludan, would result in isolation of cells that are not enucleated, i.e. still have their nuclei, and hence their DNA. Accordingly, It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of Paludan et al. for the isolation of skin cells by using such cells in the detection methods taught as being routine in the art by Frayne. The person of ordinary skill in the art would have been motivated to do so to attain the known advantages of the ease of isolation of cells as taught by Paludan. Accordingly, the invention, taken as a whole, is *prima facie* obvious over the prior art.

Claims 92, 94 102, 128 and 134 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paludan et al., J. Invest. Derm. 99:830-835, 1992 (in the case of claims 128 and 134 in view of van der Molen), and further in view of Ramsey et al., U.S. Patent Number 6,056,859 and Furcht et al., U.S. Patent Number 6,054,277.

The teachings of Paludan et al. are discussed above. Paludan did not specifically teach the use of chips. Ramsey et al. and Furcht et al. both teach the use of chips for nucleic acid sequence analysis. The stated benefits of the technologies are speed and reduced cost. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the methods of Paludan et al. to include analysis using chips as taught by Ramsey et al. and Furcht et al. for the purpose of attaining the known and expected benefits of the chip technology. Accordingly, the invention, taken as a whole, is *prima facie* obvious over the prior art.

Advisory Information:

No claim is allowed.

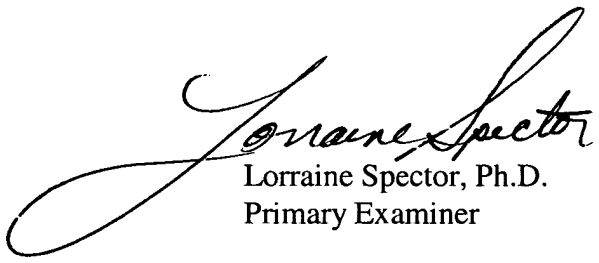
Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 5:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary L. Kunz, at (703)308-4623.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 872-9306 (before final rejection) or (703)872-9307 (after final). Faxed draft or informal communications with the examiner should be directed to (703) 746-5228.



Lorraine Spector, Ph.D.
Primary Examiner

09/375609.s1
12/10/02